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Category:

Study type: Systematic review and meta-analysis

Author's declarative title: The risk of adverse obstetric outcomes following treatment for cervical pre-invasive disease increases with cone depth.

Citation: Kyrgiou M, Athanasious A, Paraskevaïdi M, Mitra A, Kalliala I, Martin-Hirsch P, Arbyn M, Bennett P, Paraskevaïdis E. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. *BMJ* 2016;**354**:i3633

Commentary (720 words, references 154)

Context

A strong and consistent association between treatment for cervical disease and subsequent preterm birth has been established.¹ The association with preterm birth is stronger when more aggressive forms of treatment (e.g. knife cones) are considered.¹ Several studies have shown a biologic gradient, with a greater risk of preterm delivery with increasing amount of tissue removed.^{2,3} Two meta-analyses have assessed the importance of the comparison group when assessing the risk of preterm birth^{4,5} but they did not consider the amount of tissue removed. This systematic review and meta-analysis examines the impact of various types of treatment for cervical pre-invasive disease on obstetric outcomes and how this risk could be modified by the cone depth and comparison group.

Methods

This was a review of observational cohort studies that reported obstetric outcomes in women who had received local treatment for cervical intraepithelial neoplasia (CIN) compared with outcomes in women who have not been treated. Both excisional and ablative treatments were considered. There were three comparison groups: 1) general population (external), 2) self-matching before and after treatment (internal), 3) women referred to colposcopy but not treated. The main maternal outcomes included spontaneous and iatrogenic prematurity (<37, <32-34 and <28-30 gestational weeks), premature rupture of membranes (PROM) and chorioamnionitis. Several neonatal outcomes and heterogeneity were also assessed. The review clearly stated the question being addressed, the search strategy, study selection, assessment of study quality, data extraction and synthesis, and it adhered to recognised protocols from The Cochrane Collaboration and PRISMA. The results are reported as relative risks (RR) estimates and associated confidence intervals (CI).

Findings

A total of 71 studies including 65,082 treated and 6,292,563 untreated women were eligible. The risk of preterm birth increased with increasing cone depth from RR 1.54 (95% CI:1.09-2.18) for excisions of ≤10-12mm to RR 4.91 (95% CI:2.06-11.68) among those with excisions ≥20mm compared to untreated women. Women who are investigated for cervical disease (regardless of whether they go on to be treated or not) are at higher risk of preterm birth than the general population (RR 1.24, 95% CI:1.14-1.35). Therefore the comparator group modified the effect of treatment. Using the external comparator produced the highest risk of preterm birth (1.93, 95% CI:1.71-2.17) and the lowest risk was observed when the comparator group was women referred to colposcopy but not treated (1.27, 95% CI:1.14-1.41). When the comparator group was women referred to colposcopy but not treated the RR for excisions ≤10-12mm deep became non-significant (1.11, 95% CI:0.85-1.43); however the trend with increasing depth remained significant regardless of the sub-analysis performed.

Commentary

This meta-analysis confirms that the comparison group is important when assessing the risk of preterm birth because women investigated for cervical disease have a higher baseline risk of preterm birth than the general population. Further there is a clear biological gradient with increasing depth of excision that remains regardless of the comparison group used.

Several issues remain unclear. Both here and in another⁴ meta-analysis most of the heterogeneity was explained by the comparator group (and the treatment type / quality of the study), suggesting that combining studies with different comparator groups may make result difficult to interpret as they pool results from women with different baseline risks. For example, the relative risk for excisions of ≤ 10 -12mm became statistically insignificant when women referred to colposcopy but not treated were the comparator. This indicates that a small excision may not increase the risk of preterm birth among this population. Nevertheless debate remains as to what the safe cut-off for depth is, if one exists. The comparator population should be kept in mind when interpreting other results such as the effect of ablative treatments.

Some have queried whether the observed biological gradient is due to the removal of tissue or to the grade of CIN for which the woman was treated, i.e. are women with CIN2+ at greater risk regardless of the treatment. The authors comment that no firm conclusions could be drawn from the meta-analysis as only three studies included untreated women with high-grade CIN and results had wide CI (RR 1.37, 95% CI:0.85-2.19).

Implications for practice

Clinicians should be aware of the comparator group when discussing risk of preterm birth with women about to undergo treatment for CIN. Women with a history of an excision ≥ 15 mm should be identified during pregnancy and managed in the knowledge that they are at moderately increased risk of preterm birth.⁶

Commentator details

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References

1. Kyrgiou M, Koliopoulos G, Martin-Hirsch PL, et al. Obstetric Outcome after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 2006;367:489-98.
2. Sadler L, Saftlas A, Wang W, et al. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. *JAMA* 2004;291(17):2100-6.
3. Noehr B, Jensen A, Frederiksen K, et al. Depth of cervical cone removed by loop electrosurgical excision procedure and subsequent risk of spontaneous preterm delivery. *Obstet Gynecol* 2009;114(6):1232-8.
4. Conner SN, Frey HA, Cahill AG, et al. Loop electrosurgical excision procedure and risk of preterm birth: a systematic review and meta-analysis. *Obstet Gynecol* 2014;123(4):752-61.
5. Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. *BJOG* 2011;118(9):1031-41.
6. Sasieni P, Castanon A, Landy R, et al. Risk of preterm birth following surgical treatment for cervical disease: executive summary of a recent symposium. *BJOG* 2016;123(9):1426-9.

Competing interests

None